Systemic Oxidative Stress in Asthma, COPD, and Smokers

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An imbalance between oxidants and antioxidants is proposed in smokers and in patients with airways diseases. We tested this hypothesis by measuring the Trolox equivalent antioxidant capacity (TEAC) of plasma and the levels of products of lipid peroxidation as indices of overall oxidative stress. The plasma TEAC was markedly reduced (0.66 ± 0.07 mmol/L; mean ± SEM; n = 11), with increased levels of lipid peroxidation products, in healthy chronic smokers as compared with healthy nonsmokers (1.31 ± 0.10 mmol/L, n = 14, $p < 0.001$), an effect that was exaggerated in those who had smoked 1 h before the study. Plasma TEAC was also low in patients presenting with acute exacerbations of chronic obstructive pulmonary disease (COPD) (0.46 ± 0.10 mmol/L, n = 20, $p < 0.001$) or asthma (0.61 ± 0.05 mmol/L, n = 9, $p < 0.01$) with increases in plasma lipid peroxidation products. There was a negative correlation between superoxide anion release by stimulated neutrophils and plasma antioxidant capacity ($r = -0.73$, $p < 0.001$) in patients with acute exacerbations of COPD. The profound decrease in TEAC was associated with a decreased plasma protein sulfhydryl concentrations in acute exacerbations of COPD but not in smokers or in asthmatic subjects. Therefore smoking, acute exacerbations of COPD, and asthma are associated with a marked oxidant/antioxidant imbalance in the blood, associated with evidence of increased oxidative stress. The decreased antioxidant capacity in plasma may result from different mechanisms in these conditions. Rahman I, Morrison D, Donaldson K, MacNee W. Systemic oxidative stress in asthma, COPD, and smokers.

AM J RESPIR CRIT CARE MED 1996;154:1055–60.

Exacerbations of obstructive airway diseases, whether asthma or chronic obstructive pulmonary disease (COPD), are among the most common emergency admissions to hospitals and place a large burden on health resources (1). There has been considerable interest in the hypothesis that an oxidant/antioxidant imbalance may be important in the pathogenesis of asthma (2) and COPD (3). Smoking continues to be the main etiologic factor in COPD. Circulating leukocytes in smokers (4), asthmatic individuals (5), and in patients with stable COPD (6) have an enhanced oxidative burst. There is also evidence of increased neutrophil sequestration in the pulmonary microcirculation in smokers (7), in acute exacerbations of COPD (8), and following inhalation of platelet activating factor (PAF) (9), an inflammatory mediator that when inhaled by normal subjects produces effects that mimic many of the features of acute asthma. Additionally, inhaled oxidants from cigarette smoke (estimated to be 10^{14} free radicals/puff and up to 300 to 500 ppm of nitric oxide [NO] and nitrogen dioxide [10, 11]) or oxidants released from alveolar leukocytes (12) contribute to the increased oxidant burden in these conditions. Fortunately, the lungs have an extensive and potent antioxidant defense system, present both extra- and intracellularly, which protects lung cells from oxidant damage (13). There is conflicting evidence for the presence of an absolute or functional antioxidant deficiency in the air spaces of smokers or patients with COPD, depending on which antioxidant is studied (14–16). There is also a hypothesis that links exacerbations of asthma to dietary antioxidant deficiency (17).

An oxidant/antioxidant imbalance in favor of oxidants can lead to lung injury due to direct, unprotected oxidative damage to air space epithelial cells (18). Additionally, such injury could be indirect, via oxidative inactivation of antiproteases (19), resulting in enhanced proteolysis of lung connective tissues such as elastin, an important event in the pathogenesis of emphysema.

Reactive oxygen species, generated by neutrophils, whether circulating or sequestered in the pulmonary vasculature, are scavenged by blood antioxidants and antioxidant enzymes. Thus, the ability of an individual to prevent the injurious effects of oxidative stress depends on the antioxidant capacity of the blood and the tissues. In the study reported here, we tested the hypothesis that an oxidant–antioxidant imbalance is present in the plasma of smokers, patients with COPD, and asthmatic individuals.

METHODS

Patients/Subjects

Healthy nonsmokers/smokers. We studied two groups of healthy nonsmokers who had no history of lung diseases. The first group consisted

(Received in original form September 14, 1995 and in revised form January 16, 1996)

Supported by the Chest, Heart and Stroke Association (Scotland), the Norman Salvesen Emphysema Research Trust, and the Tobacco Products Research Trust.

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Am J Respir Crit Care Med Vol 154. pp 1055–1060, 1996

of 14 younger subjects (nine males and five females) 31 ± 7 yr and an older group of 18 subjects (eight males and 10 females) aged 59 ± 7 yr. All subjects were randomly selected from hospital staff. The younger nonsmokers were used as the control group for the smokers and the older normal subjects as a control group for the patients with COPD and asthma. Twenty healthy smokers (14 males and six females, mean age 39 ± 9 yr) with a smoking history of 19 ± 6 pack-yr and an FEV_1 of 92 ± 8% of predicted values were also studied.

Asthma patients. Twenty patients with long-standing asthma also took part in the study. Their diagnosis was made by a respiratory physician on the basis of variable breathlessness and/or wheeze and an improvement of more than 20% in FEV_1 following nebulised β_2 agonist. All were nonsmokers (10 males and 10 females aged 55 ± 3 yr; FEV_1 71.3 ± 21.2% of predicted values). Nine patients were studied when clinically stable, at least 1 mo after an exacerbation. Their medication consisted of β_2 agonists, inhaled corticosteroids, and in some cases ipratropium bromide. None of the patients were receiving oral corticosteroids or theophylline preparations. Eleven asthma patients were studied within 3 h of admission to the hospital with an acute exacerbation of their condition. Six of these patients had received oral corticosteroid therapy (20 to 40 mg prednisolone) in the week before admission. All received oral corticosteroids (40 mg prednisolone) and nebulized bronchodilators during their admission.

Patients with COPD. Twenty-nine patients with COPD (18 males and 11 females, mean age 69 ± 4 yr) were enrolled from the respiratory outpatient clinic. The diagnosis was made by a respiratory physician on the basis of current or former smoking and severe, largely irreversible (< 15% improvement in baseline FEV_1 following nebulized β_2 agonist) airflow limitation (FEV_1 = 30.9 ± 2.8% of predicted values). Their clinical condition was stable, with no acute exacerbations of COPD for 1 mo prior to the study.

Twenty patients (12 males and eight females, mean age: 67 ± 2 yr) who presented with an acute exacerbation of COPD were also studied. Eleven of the 20 patients had been started on corticosteroid therapy (20 to 40 mg prednisolone) during the week before admission. Prior to admission, these patients' other medications consisted of inhaled steroids and bronchodilator therapy in the form of β_2 agonists, ipratropium bromide, and/or theophyllines. On admission, the patients' Pa_{CO_2} during breathing of air was 8.0 kPa ± 1.2 kPa (mean ± SD). None of the patients had clinical or radiologic evidence of a pneumonia.

Blood samples were taken from four of the normal subjects on three separate occasions separated by 1 and 7 d, respectively. Smokers had venous blood withdrawn when they had not smoked a cigarette for 12 h before the study (chronic smokers: n = 11), or 1 h after smoking two cigarettes (acute smokers: n = 9). In these studies plasma was obtained by centrifugation (250 × g) of lithium-heparinized blood and analyzed immediately.

Patients with COPD and those with asthma were studied when clinically stable, as described earlier, or within 3 h of admission to the hospital with an acute exacerbation of their condition, and in some cases again at the time of discharge (5 to 10 d later).

The study had the approval of our local ethical committee.

Neutrophil Harvesting

Thirty milliliters of blood were withdrawn from normal, healthy nonsmokers and patients with COPD or asthma, mixed with Dextran (70 kDa; Travenol Laboratories, Norfolk, UK), and allowed to sediment for 1 h. The resulting leukocyte-rich plasma was overlaid on a plasma/Percoll density gradient (Pharmacia, Uppsala, Sweden) and centrifuged to obtain a neutrophil band that was washed and lysed to remove contaminating erythrocytes, using a technique we have described previously (8). The harvested neutrophil population was more than 95% pure and was resuspended in phosphate-buffered saline (PBS) at a concentration of 1 × 10^7 cells/ml. The viability of neutrophils harvested with this technique was > 98% by Trypan blue exclusion. The platelet-poor plasma obtained during the course of the harvesting procedure was used for the antioxidant capacity, lipid peroxides, protein sulfhydryl, and protein carbonyl assays.

Superoxide Anion Assay

Superoxide anion (O_2^-) generation by neutrophils (2.5 × 10^5 cells) was measured as the superoxide dismutase (SOD)-inhibitable reduction of cytochrome C (20). Release of O_2^-, either spontaneously or when stimulated with phorbol myristate acetate (PMA 1 μg/ml), was measured after incubation for 80 min. The difference in absorbance of the supernatant fluids, in the presence or absence of SOD, was determined with a Pye Unicam 8700 spectrophotometer (Unicam Analytical Systems, Cambridge, UK) at 550 nm. The amount of reduced cytochrome C was calculated on the basis of an extinction coefficient of 21.0/mM/cm for cytochrome C.

Trolox Equivalent Antioxidant Capacity

In order to measure the Trolox equivalent antioxidant capacity (TEAC) of plasma, 10 ml of venous blood was withdrawn into a lithium-heparin tube and centrifuged, and the plasma removed and analyzed immediately. The plasma antioxidant capacity was measured by the method of Miller and coworkers (21). The TEAC was calculated by defining the concentration, in mmol/L, of Trolox having antioxidant capacity equivalent to a 1.0 mmol/L sample of the plasma under investigation. The components of plasma that contributed to the TEAC in percentage terms were albumin, 43%; urate, 33%; ascorbate, 9%; α-tocopherol, 3%; bilirubin, 2%; and remaining antioxidants, 10% (21).

Lipid Peroxides Assay

The level of plasma lipid peroxidation products as thiobarbituric acid (TBA)–malondialdehyde (MDA) adducts was measured spectrophotometrically by the method described by Yagi (22). The final result was expressed as micromoles of MDA formed per liter of plasma.

Protein Sulfhydryl and Protein Carbonyl Assays

Protein thiols were measured using the method of Ellman (23). Oxidized protein sulfhydryls were measured by treating acute COPD plasma with 10 mM dithiothreitol (DTT), at 4° C for 2 h, followed by dialysis overnight at 4° C against 2 × 100 volumes of nitrogen-saturated PBS. Reduced protein sulfhydryls were then measured with Ellman's reagent as described earlier (23).

Protein carbonyls were assayed by the method described by Rodney and coworkers (24).

Statistical Analysis

The data are expressed as mean ± SEM, unless otherwise stated. Differences between mean values were assessed by analysis of variance (ANOVA).

RESULTS

Normal Subjects

In normal subjects there was no significant correlation between the TEAC in plasma and age (n = 32, r = 0.35, $p > 0.05$). The results of repeated measurements of TEAC in the plasma of four normal subjects are shown in Table 1. There was no significant difference in the mean values of the three measurements.

Smokers

Compared with normal subjects, chronic smokers had lower levels

TABLE 1

DAY-TO-DAY VARIATION OF PLASMA TEAC IN NORMAL HEALTHY INDIVIDUALS

	Time (d)		
Subject	0	1	7
1	1.30	1.14	1.36
2	1.32	1.23	1.26
3	1.32	1.20	1.39
4	1.26	1.17	1.19
Mean ± SE	1.32 ± 0.01	1.18 ± 0.01	1.3 ± 0.05

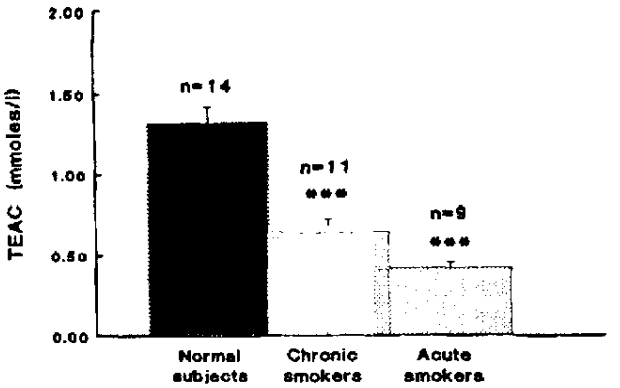

Figure 1. Effects of smoking on plasma antioxidant capacity (TEAC). The histograms represent the mean and the bars the SEM. ***$p < 0.001$ *compared with normal subjects.*

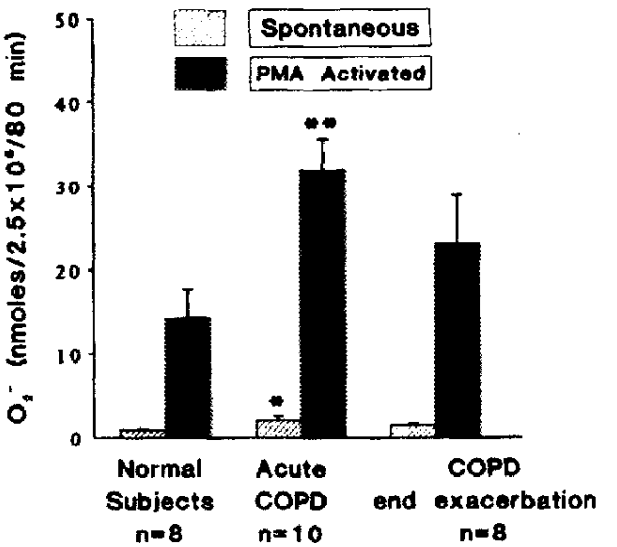

Figure 2. Spontaneous and PMA-stimulated superoxide anion (O_2^-) release from peripheral blood neutrophils from normal subjects and patients with acute exacerbations of COPD (*acute*), and at the end of the exacerbation (*end exacerbation*). The histograms represent the means and the bars the SEM. *$p < 0.05$; **$p < 0.01$ compared with normal subjects.

of TEAC in plasma, which were even lower 1 h after smoking one cigarette (Figure 1). Products of lipid peroxidation in plasma were higher in smokers than in nonsmokers, but protein sulfhydryl and protein carbonyl levels in plasma were similar (Table 2).

COPD

The spontaneous generation of O_2^- from neutrophils from patients with acute exacerbations of COPD was significantly greater than in healthy, age-matched subjects (Figure 2). The difference in O_2^- generation between normal subjects and patients with acute exacerbations of COPD was more pronounced when measured after stimulation with PMA. Both the spontaneous and stimulated neutrophil release of O_2^- returned to control values when the patients were restudied 5 to 10 d later, at the time of discharge, when their condition had stabilized.

The TEAC in plasma was similar in normal subjects and patients with COPD who were clinically stable (Figure 3). Among these patients, however, those who were former smokers had higher levels of plasma TEAC (1.30 ± 0.10 mmol/L, mean ± SEM, n = 6) than those who were smokers (1.07 ± 0.09 mmol/L, n = 19, $p < 0.05$).

The plasma TEAC levels in the patients presenting with acute exacerbations of COPD were much lower than those in healthy, age-matched normal subjects or patients with stable COPD (Figure 3). Those patients with acute exacerbations of COPD who were treated with prednisolone prior to admission had plasma TEAC levels (0.53 ± 0.09 mmol/L, n = 9) similar to those of patients who did not receive prednisolone (0.40 ± 0.06 mmol/L, n = 11, $p > 0.05$). In seven of these patients who were restudied after treatment at the end of their exacerbation, when their condition was stable, the antioxidant capacity in plasma had increased from 0.49 ± 0.09 mmol/L to 0.99 ± 0.19 mmol/L ($p < 0.001$).

Plasma levels of lipid peroxidation products, measured as TBA-MDA derivatives, were higher in patients with COPD than in normal subjects, and were highest in those patients presenting with an exacerbation of COPD (Table 2). Compared with age-matched normal subjects, protein sulfhydryl levels were sig-

TABLE 2

LEVELS OF LIPID PEROXIDES/PROTEIN SULFHYDRYLS AND PROTEIN CARBONYLS IN PLASMA FROM SMOKERS AND PATIENTS WITH COPD AND ASTHMA

	Normal Healthy Nonsmokers		Smokers		COPD		Asthma	
	Young	Old	Acute	Chronic	Acute	Stable	Acute	Stable
n	14	18	9	7	11	9	11	9
Lipid peroxides [TBARS], μmol malondialdehyde/L	1.4 ± 0.2	1.3 ± 0.1	3.4 ± 0.5‡	2.5 ± 0.4†	3.1 ± 0.6‡	2.0 ± 0.3†	4.6 ± 0.8‡	2.2 ± 0.4*
n	12	12	9	7	11	9	11	9
Protein sulfhydryls, mmol/L	0.51 ± 0.11	0.52 ± 0.06	0.48 ± 0.05	0.49 ± 0.06	0.32 ± 0.04‡	0.44 ± 0.05	0.37 ± 0.06	0.40 ± 0.04
n	8	6	9	11	15	8	11	9
Protein carbonyls, nmols/mg protein	0.45 ± 0.04	0.40 ± 0.08	0.43 ± 0.06	0.46 ± 0.07	0.40 ± 0.05	0.38 ± 0.06	0.40 ± 0.06	0.38 ± 0.04

* $p < 0.05$.
† $p < 0.01$.
‡ *$p < 0.001$; for smokers compared with young nonsmokers; for COPD and asthma compared with old nonsmokers; acute smokers, patients with COPD and asthma had significantly* higher levels of lipid peroxides than patients with the corresponding chronic states ($p < 0.05$).
Platelet poor plasma was used for the assays (see METHODS).

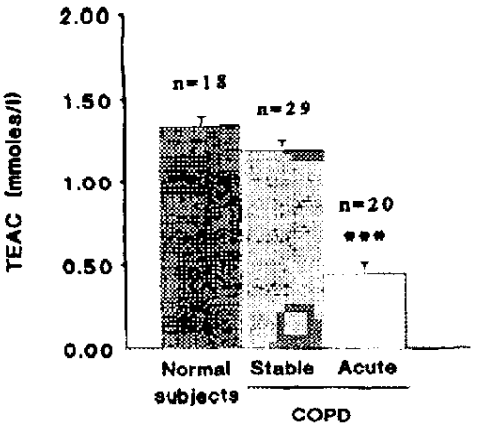

Figure 3. Plasma antioxidant capacity (TEAC) in patients with stable and acute COPD. The histograms represent the mean and the bars the SEM. ***$p < 0.001$ compared with normal subjects.

nificantly lower in patients presenting with an acute exacerbation of COPD, but not in patients with clinically stable COPD (Table 2). The lower levels of plasma protein sulfhydryls that were present in patients with acute exacerbations of COPD were partially restored after treating plasma with the reducing agent DTT (acute COPD: 0.33 ± 0.04 mmol/L; acute COPD plasma treated with DTT: 0.39 ± 0.04 mmol/L; $n = 7$, $p < 0.05$) compared with normal subjects (0.54 ± 0.06, $n = 12$). The plasma albumin level in these patients was 39.1 ± 4.3 g/L (mean ± SEM), which was not significantly different from that in normal subjects (40.3 ± 6.4 g/L, $p > 0.05$). Protein carbonyls were not different between the groups.

In patients presenting with an acute exacerbation of COPD, we found significant inverse correlations between plasma TEAC and PMA-induced neutrophil O_2^- release ($n = 10$, $r = -0.73$, $p < 0.001$), and a positive correlation between plasma TEAC and Pa_{O_2} when the patients were breathing air ($n = 12$, $r = 0.95$, $p < 0.001$). There was also a significant correlation between protein sulfhydryls and TEAC ($n = 11$, $r = 0.68$, $p < 0.001$).

Asthma

In clinically stable asthmatic patients, plasma TEAC was lower than in age-matched normal subjects, and was even lower in those who were studied during an exacerbation of their condition (Figure 4). Although there was a trend for TEAC values to improve by the time of discharge (0.84 ± 0.12 mmol/L, mean ± SEM, $n = 7$) as compared with values on admission (0.61 ± 0.05 mmol/L, $n = 11$), this change was not significant ($p = 0.18$). The plasma levels of products of lipid peroxidation, measured as TBA-MDA adducts, were significantly higher in chronic asthmatic patients and even higher in those with acute asthma as compared with age-matched normal subjects (Table 2). However, there were no differences in the protein sulfhydryl or protein carbonyl levels in patients with acute or stable asthma as compared with the levels in normal subjects (Table 2).

DISCUSSION

There has been considerable interest in the concept that an oxidant–antioxidant imbalance has a role in the pathogenesis of lung diseases, particularly emphysema (25) and asthma (2). Evidence for a reduction in antioxidants in the distal air spaces of smokers or patients with COPD varies, depending on the antioxidant measured. For example, vitamin E is low in the bronchoalveolar lavage fluid (BALF) of smokers as compared with nonsmokers (15), whereas glutathione levels are increased (14). Moreover, leukocytes from smokers release more reactive oxygen species (4), although the acute effect of smoke could inhibit the release of reactive oxygen species from neutrophils (26). The apparently contradictory results of these studies may arise from the problems of sampling either cells or fluid from the air spaces by bronchoalveolar lavage (BAL) (27).

In asthma, an increased oxidant burden is thought to result from the release of reactive oxygen intermediates from circulating or air space leukocytes (28, 29), but also from the release of nitric oxide (NO) (30). Superoxide anion and NO react very rapidly to form peroxynitrite, which has potent oxidant properties (11, 30).

Clinical studies of the oxidant–antioxidant balance have focused on the chronic effects of smoking, COPD, or asthma, whereas the confounding effects of acute smoking or acute exacerbations of these conditions have received much less attention. Thus the role of an oxidant–antioxidant imbalance in lung diseases remains unproven (31).

We became interested in measuring the effects of oxidative stress in the blood of smokers and patients with acute exacerbations of COPD following our observations that increased numbers of neutrophils were sequestered in the pulmonary microvasculature under these circumstances (7, 8). Furthermore, we have shown in animal studies of acute lung inflammation that sequestered neutrophils are primed to release reactive oxygen species (32). Thus our hypothesis was that the increased numbers of inflammatory leukocytes in the bronchoalveolar space, and/or those sequestered in the pulmonary microvasculature during smoking and in acute exacerbations of COPD (7, 8) and asthma (9, 29), may create an increased oxidant burden, the effects of which could be detected in plasma as an increase in markers of oxidant stress.

We tested this hypothesis by measuring changes in the antioxidant capacity of plasma, by comparing the antioxidant capacity of the potent antioxidant Trolox with that of plasma through measurment of the TEAC, an assay recently described by Miller and coworkers (21). We found no relationship between plasma antioxidant capacity and age in normal subjects, which is contrary to data from measurements of plasma antioxidants in other

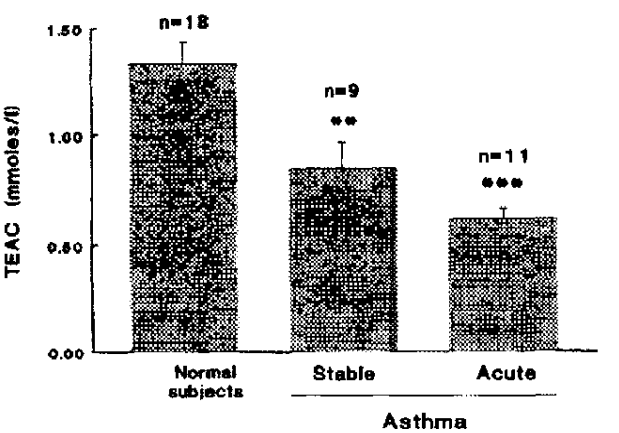

Figure 4. Plasma antioxidant capacity (TEAC) in patients with stable and acute asthma. The histograms represent the mean and the bars the SEM. **$p < 0.01$; ***$p < 0.001$ compared with normal subjects.

studies (33). However, there was a lower antioxidant capacity in the plasma of chronic smokers, and more pronouncedly in that of acute smokers, than in age-matched healthy nonsmokers. The effect of smoking was also reflected in patients with clinically stable COPD, who as a group had a normal plasma antioxidant capacity. However, those who were current smokers had lower plasma antioxidant capacity than those who were former smokers.

Furthermore, we found a marked reduction in antioxidant capacity in the plasma of patients presenting with acute exacerbations of COPD or asthma as compared with age-matched normal subjects. The TEAC values in the plasma of patients who had received corticosteroids prior to their admission with an acute exacerbation were not different from those who had not received corticosteroids. However, the plasma TEAC returned to normal values after treatment in patients with acute exacerbations of COPD at a time when the patient's condition was stable enough to allow discharge from the hospital. The same was not true for patients with acute asthma. These data are supported by the plasma TEAC values, which were normal in patients with stable COPD but low in those with chronic but stable asthma. These results suggest the presence of increased oxidative stress in the plasma of patients with acute exacerbations of COPD and asthma, with an equivalent decrease in the two groups' antioxidant capacity during acute smoking. They also suggest that continued oxidant stress occurs in chronic smokers and in patients with stable but chronic asthma, but not in clinically stable patients with COPD.

Further evidence for an increased oxidant stress comes from the levels of lipid peroxidation products in smokers and patients with COPD and asthma, which were higher than in normal subjects. The values were also higher in the acute condition than in the chronic or stable groups of patients or smokers. Although TBA-MDA adducts are nonspecific products of lipid peroxidation, the changes in the different groups are so striking that we believe that these changes represent further evidence of oxidant stress in plasma. Increased plasma levels of products of lipid peroxidation have been reported in smokers (34). Therefore, our data provide further evidence of persistent, increased oxidant stress in the plasma in all of the foregoing groups as compared with normal subjects.

Others have demonstrated increased release of oxidants from circulating leukocytes in asthma patients (5) and smokers (4). The present study also shows priming of circulating neutrophils in acute exacerbations of COPD. In addition, the increased superoxide anion release from neutrophils observed in the study correlated with the decrease in plasma antioxidant capacity in patients with acute exacerbations of COPD. Thus, the release of reactive oxygen intermediates from circulating or sequestered neutrophils may be a major source of oxidant stress, leading to a reduction in antioxidant capacity in plasma in acute exacerbations of COPD. The data of Miller and colleagues (21) suggest that TEAC values in plasma are influenced by a number of antioxidants such as albumin, urate, and glutathione. Our data suggest that the plasma component that is associated with the reduction in TEAC is different in smokers, asthmatic individuals, and patients with COPD. In acute COPD the reduction in TEAC appears to be due at least in part to a decrease in protein sulfhydryl groups, as shown by the correlation between these two variables without any change in plasma albumin. Furthermore, our preliminary data suggest that the decrease in the protein sulfhydryl concentration in the plasma of acute COPD patients was at least in part due to the oxidation of sulfhydryl groups, since DTT treatment produced a partial but significant recovery of protein sulfhydryls. Accordingly, the mechanism producing the decrease in TEAC in these conditions may also be different. Further studies, measuring individual antioxidants and oxidized protein-SH in plasma, are in progress to answer this question.

An earlier study by Taylor and colleagues (3) used an indirect and complex assay of antioxidant activity, measured as the enzymatic oxidation of the plasma elastase inhibitory capacity, to investigate antioxidant capacity in COPD. Using this technique, Taylor and colleagues described a deficiency in the antioxidant activity of plasma and increased ceruloplasmin levels in patients with stable COPD. However, their assay excludes several major antioxidant molecules. In the present study we used a simple, rapid, direct, and stable spectrophotometric method to assay the total antioxidant capacity in the plasma as the TEAC, which is dependent on various plasma antioxidants, including albumin-SH, as discussed in the METHODS section. Our data extend the observations of Taylor and coworkers (3) to patients with acute exacerbations of COPD, asthma, and smokers. The data also demonstrate a relationship between Pa_{O_2} and TEAC in patients with acute exacerbations of COPD. This may simply reflect the severity of the exacerbation or may relate to priming of neutrophils by hypoxemia (35).

There was no clear evidence that treatment with steroids altered the antioxidant capacity in patients with exacerbations of COPD or asthma. However, treatment with steroids both before and after admission was given in an uncontrolled way on the advice of the general practitioner or attending hospital physician. A beneficial effect of long-term corticosteroids on lung function in patients with chronic airflow obstruction has been suggested (36). Evidence from *in vitro* studies also suggests that among the antiinflammatory actions of steroids are a reduction in the generation of reactive oxygen species by neutrophils (37) and stimulation of the synthesis of glutathione in liver (38). However, the possible role of steroids in inducing a recovery of antioxidant capacity in patients with acute exacerbations of COPD and asthma remains speculative.

There have been no new therapies for acute exacerbations of COPD or asthma over the past two decades. The new observations in this study strongly suggest that an oxidant-antioxidant imbalance that may have therapeutic implications occurs in these conditions. Similarly, the accumulating evidence for an oxidant-antioxidant imbalance in asthma (2) is strengthened by the results of this study, which indicate a profound decrease in antioxidant capacity and an increase in markers of oxidant stress in asthma, suggesting that a clinical trial of an intervention to enhance antioxidant levels in asthma is worth pursuing.

In summary, our results provide new evidence for a profound oxidant-antioxidant imbalance in smokers, patients with acute exacerbations of COPD, and patients with chronic and acute asthma. The relationship between the decrease in antioxidant capacity in plasma and the pathogenesis of the acute exacerbations of these conditions requires further study.

Acknowledgment: The authors thank Dr. N. J. Miller for his helpful advice on the TEAC assay. They also thank Eileen Neal for typing the manuscript.

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